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# HIV Co-Infections with Hepatitis B and C

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**Abstract**

With the introduction of highly active antiretroviral therapy (HAART), Human Immunodeficiency Virus (HIV) infected patients live longer and many have co-infections with chronic hepatitis B (HBV) or hepatitis C (HCV) that complicates their care. Treatment of HBV and HCV in the HIV positive co-infected patient requires careful consideration of the timing of initiation of HAART treatment, drug-drug interactions and drug and immune effects. It is an exciting era due to the introduction of new medications available to treat both HBV and HCV infections. Knowledge of the complex interactions between these viruses as well as the effect of various treatment modalities on each virus is the key to understanding and treating these patients effectively.

## Introduction

Highly active antiretroviral therapy (HAART) for the Human Immunodeficiency Virus (HIV) infected patient has ushered in an era of declining opportunistic infections and led to a new focus on other leading causes of morbidity, such as end-stage liver disease (ESLD) secondary to hepatitis B virus (HBV) and hepatitis C virus (HCV) infection [1]. We will review the interactions between HIV and HBV and HCV co-infections as well as their epidemiology, pathogenesis, laboratory evaluation and recent updates in treatment options.

## Hepatitis B Co-Infection

HBV does not change the course of HIV disease, but HIV does alter the course of HBV [2]. Patients with chronic HBV infection were 3.5 times more likely to have liver disease than those with no HBV infection ($P<0.02$) [3]. HIV infected persons are less likely to clear acute HBV infection spontaneously and face a higher risk of liver-related death than those who are infected with only HIV [4]. The presence of chronic HBV can also lead to an increased risk of hepatotoxicity related to the administration of HAART. Individuals co-infected with HIV and HBV, especially those with low cluster of differentiation 4 (CD4) T lymphocyte nadir counts, are at increased risk for liver-related mortality [5]. Management of HBV in co-infected patients is complicated not only by the differences in natural history, but also, by the activity of many of the drugs active against both viruses and by the development of drug-resistant HIV and HBV variants.

## Epidemiology

HBV is a deoxyribonucleic acid (DNA) virus. In the United States, the prevalence of chronic carriage of hepatitis B surface antigen (HBsAg) is present in less than 1% of the population [6,7]. In HIV infected individuals, this prevalence is approximately 10-20 folds higher [8,9]. In a US study examining 16,248 HIV-infected patients, the prevalence of chronic HBV was seen in 8 percent of unvaccinated participants [10]. A higher prevalence was found in non-Hispanic men especially in men who have sex with men (MSM) and in those who were aged 35-44 [9]. In the United States and Western Europe, HBV is typically acquired during sexual activity in adolescence or early adulthood. On the other hand, in Asia and sub-Saharan Africa, perinatal transmission is more common with chronic HBV infection present in 90% of exposed infants [11]. HBV infection in HIV infected patients increases the risk of cirrhosis, ESLD and death from liver disease, especially in patients with a low CD4 cell count or concomitant alcohol use [5].

Liver disease related to infection with HBV is a frequent cause of morbidity and mortality in those infected with HIV. HIV and HBV infections share similar transmission patterns and risk factors such as intravenous drug users (IVDU) and sexually transmitted diseases (STD). In developed countries, laboratory markers of prior HBV infection are more common in MSM and IVDU [10,12,13].

## HBV genotypes

Eight HBV genotypes have been identified as A through H [14,15]. The prevalence of each HBV genotype depends on the geographical location. All known HBV genotypes have been found in the United States with the following prevalence: A (35%), B (22%), C (31%), D (10%) and E-G (2%) [16]. While HBV genotype A is the most common in co-infected individuals, the non-A genotypes were associated with more advanced fibrosis [17]. Furthermore, Genotypes B and C were associated with higher viral loads than were types A and D [18].

## Pathogenesis

There are many potential reasons for increased liver-related mortality in HIV and HBV co-infected individuals. In HIV infected persons, a rapidly progressive form of liver disease called fibrosing cholestatic hepatitis is seen and thought to be due to a viral cytopathic effect [19]. Revill reported a novel -1G mutation which was identified in the HBV pre-core and overlapping core genes. This mutation truncates the pre-core/core proteins. The mutant genome was the dominant species in some HIV/HBV co-infected individuals and was more prevalent in HIV/HBV co-infected individuals than HBV mono-infected individuals. The mutation was associated with higher HBV DNA concentrations in HIV/HBV co-infected individuals. Mutations in the HBV core and pre-core genes may be contributing to disease pathogenesis in HIV/HBV co-infected individuals [20]. Preiss reported defective HBV DNA (dDNA) that is reverse-transcribed from spliced HBV pre-genomic messenger RNA (pgRNA) and has been identified

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in patients with chronic HBV. The major 2.2-kb splice pgRNA encoded a novel HBV gene product, the hepatitis B splice protein (HBSP), via a deletion and frame shift within the polymerase. Although spliced RNA and HBSP expression have been associated with increased HBV DNA levels and liver fibrosis, the role of dDNA in HBV associated disease is largely undefined. Defective DNA was detected in 90% of persons with chronic HBV. There was no significant difference in the relative abundance of dDNA between the mono-infected and HIV/HBV co-infected groups [21].

Immune activation due to increased HIV induced microbial translocation may be a mechanism for accelerating liver disease. Circulating lipopolysaccharide (an indicator of microbial translocation) was significantly increased in chronically HIV-infected individuals and in simian immunodeficiency virus (SIV) infected rhesus macaques (P= 0.002). Effective antiretroviral therapy seemed to reduce microbial translocation [22].

HAART induced immune restoration may switch the immune reaction to HBV from a tolerant to an intolerant phase, leading to either the complete control of HBV replication or more often to an exacerbation of chronic hepatitis. Patients who spontaneously recover from HBV infection mount vigorous CD4 and cluster of differentiation 8 (CD8) T-cell responses to various HBV epitopes [10,23]. Lascar reported reconstitution of HBV specific T cell responses in HIV infected patients after a reduction in their HBV load. This potential to recover T cell responses, which is critical for HBV control, provides support for the addition of anti-HBV therapy in the treatment of HIV/HBV co-infected patients [24].

## Laboratory evaluation

Hepatitis B surface Antigen (HBsAg0) is the serologic hallmark of HBV infection and appears in serum one to ten weeks after acute exposure to HBV. This is followed by the detection of IgM and then IgG anti-Hepatitis B core antibody (anti-HBc). Most adults clear HBsAg and develop anti-Hepatitis B surface antibody (anti-HBs) consistent with immunity. Persistence of HBsAg for more than six months implies chronic infection and is associated with the presence of HBV DNA viremia.

Chronic hepatitis B should be evaluated further by ordering hepatitis B e antigen (HBeAg) (which is the extracellular form of the hepatitis B core Antigen (HBcAg)) and hepatitis B e antibody (anti-HBe). The HBeAg seropositive state indicates stronger viral infectivity. Hepatitis D (HDV) is a small circular enveloped ribonucleic acid (RNA) virus that requires the presence of HBV for replication. The presence of HDV is associated with more complications and a higher mortality. HDV antibodies should be checked especially in patients from Eastern Europe, the Mediterranean, and the Amazon basin who have higher rates of this.

HBV DNA (measured in copies/mL or IU/mL) is useful in monitoring therapeutic efficacy. Currently there is no specific guideline for ultrasound (US) and alpha-fetoprotein (AFP) frequency in HIV/HBV co-infected persons. The American Association for the Study of Liver Diseases (AASLD) Practice Guideline in 2009 recommended surveillance of HBV carriers at high risk of hepatocellular carcinoma (HCC) with US every 6-12 months and AFP alone when US is not available or cost is an issue [25]. However, AFP determination lacks adequate sensitivity and specificity for effective surveillance [26] and so surveillance with US every 6 months is preferred [27].

Chronic HBV activity is inferred by elevations of aminotransferases and by the presence of viremia. The presence of HBeAg not only indicates the level of infectivity but also is usually associated with higher levels of HBV DNA and active liver disease. Seroconversion from HBeAg to anti-HBe positive is usually associated with declines in serum HBV DNA and remission of liver disease. Some patients continue to have active liver disease and high levels of HBV DNA in serum even after the loss of HBeAg (HBeAg negative chronic hepatitis). These latter patients may have HBV variants that abolish or decrease the production of detectable HBeAg in serum. HIV infected patients can have high levels of HBV DNA with hepatic necrosis and inflammation when they are anti-HBc positive but HBsAg negative [28].

## Treatment

There are two chronic HBV treatment modalities namely interferon (IFN) and nucleoside reverse transcriptase inhibitors (NRTI). The latter is the mainstream therapy for HIV/HBV co-infection. The dual antiviral activity of NRTI requires careful coordination and selection in order to avoid selection of resistance mutations and toxicity. Patients who need treatment for HBV infection but not HIV infection should not receive HBV medications that have activity against HIV. Instead, they should receive agents with HBV activity alone.

## HBV treatment initiation in HIV patients

Treatment of HBV in HIV infected patients is similar to patients with HBV infection alone. In the patient with chronic HBV infection, viral replication and/or assessment of liver histopathology are helpful in determining the need for antiviral therapy. There is inadequate data in HIV/HBV co-infection to determine the appropriate cut off value for HBV DNA levels for treatment initiation but many experts recommend a threshold >2000 IU/mL (>10,000 copies/mL), as is recommended in patients with HBV alone [29].

In HIV/HBV co-infected, if HBe Ag is negative, HBV DNA <2,000 IU/ml with a normal alanine aminotransferase (ALT), then consider monitoring every 6–12 months. If HBV DNA ≥2,000 IU/ml with a normal ALT, consider liver biopsy and if fibrosis is present then consider treatment. If HBV DNA ≥2,000IU/ml with an abnormal ALT, consider treatment [25,29] (Table 1).

## Approved HBV nucleos(t)ide analogues for treatment of HBV

In HIV/HBV co-infected patients, lamuvidine (3TC) and tenofovir (TDF) in combination with a third antiretroviral is the gold standard for treating both infections together. Emtricitabine (FTC), which is used in combination with TDF (Truvada, brand name), has been associated with hepatitis flares and is not FDA approved for HBV treatment. However, many clinicians favor using this because of the activity against both HIV and HBV in one tablet. Currently, monotherapy with

| Medications | FDA approved | Dose in HIV patients | Effect on HIV |
|---|---|---|---|
| Lamuvidine | 1998 | 300 mg orally daily | Yes |
| Adefovir | 2002 | 10 mg orally daily | None |
| Entecavir | 2005 | 1 mg orally daily | Slight |
| Pegylated Interferon α-2a | 2006 | 180 mcg/wk IM (only in genotype A, B or C) | None |
| Telbuvidine | 2006 | 600 mg orally daily | None |
| Tenofovir | 2008 | 300 mg orally daily | Yes |
| Emtricitabine | Not approved | 200 mg orally daily | Yes |

**Table 1:** Treatment options for HIV/HBV co-infected.

Food and Drug Administration (FDA).

a nucleos(t)ide analogue or PEG IFN is recommended as the initial therapy in solo infected HBV patients. If only treating HBV but not HIV in a co-infected patient, Pegylated Interferon (PEG IFN), adefovir (ADV) or telbuvidine (LdT) may be used as monotherapy but ADV has weak antiviral activity [30] and LdT, like 3TC, has high rates of drug resistance. Resistance to 3TC is well recognized in HIV strains and is encoded within the tyrosine-methionine-aspartate-aspartate (YMDD) motif near to the catalytic site of reverse transcriptase [31]. HBV resistance to 3TC was reported to be 50% after 2 years and 90% after 4 years of therapy in a retrospective cohort study of HIV/HBV co-infected persons [32,33]. Anti-HBe seroconversion and HBeAg seronegativity were observed in 11% and 18.5% of cases, respectively in 3TC treated patients. Factors associated with an increase rate of 3TC resistance include long treatment duration, high pre-treatment serum HBV DNA levels and high residual virus levels after initiation of treatment [34,35]. ADV is the only extensively studied therapeutic alternative for 3TC resistant HBV infection in HIV/HBV co-infection. *In vitro* and clinical studies showed that ADV is effective in suppressing wild type as well as 3TC resistant HBV [36]. LdT is more potent than 3TC in reducing the HBV DNA levels after one year of therapy [37]. There were some concerns regarding activity of LdT with HIV but a recent study showed that LdT has no activity against HIV *in vitro* [38].

Entecavir (ETV), TDF, 3TC and FTC should not be used as monotherapy for HBV in an infected HIV patient since they have anti-HIV activity and can lead to rapid HIV resistance. ETV is a potent antiviral therapy for the treatment of HBV infection. Initially, it was believed that this agent did not have activity against HIV infection. However, subsequent clinical and *in vitro* data showed that use of ETV in an HIV infected patient with detectable HIV RNA can lead to an M184V mutation which confers drug resistance to 3TC and FTC [39,40,41]. ETV should only be used to treat HBV in the HIV infected patient who has attained complete viral suppression. ETV has not been evaluated in patients with HIV and HBV co-infection who are not receiving effective treatment for HIV at the same time. TDF is a nucleotide reverse transcriptase inhibitor and it has been shown to have potent *in vitro* activity against both wild type and 3TC resistant HBV [42]. The Department of Health and Human Services (DHHS) guidelines suggest inclusion of TDF plus either 3TC or FTC in the antiretroviral regimens of patients co-infected with HIV and HBV who require treatment for their HIV infection. FTC (although not FDA approved for HBV) is a potent inhibitor of both HIV and HBV replication and has a longer serum half-life than 3TC.

PEG IFN is not recommended for patients with hepatic decompensation, immunosuppression, medical or psychiatric contraindications. PEG IFN may be used in compensated cirrhotic patients who have normal synthetic function and no evidence of portal hypertension. Nucleos(t)ide analogues may be used in patients with decompensated liver disease, contraindications to PEG IFN, ability to commit to long durations of treatment and in patients with low CD4 cell counts (<200cells/μl). ETV and TDF have the best safety, efficacy and drug resistance profiles. TDF is preferred in patients contemplating pregnancy and in patient previously exposed to 3TC or LdT. ETV is preferred in patients with renal insufficiency.

## Management of HBV antiviral drug resistance

Emergence of antiviral drug resistance is manifested by virologic breakthrough, defined as an increase in serum HBV DNA levels of >1 $\log_{10}$copies/mL from nadiror the detection of HBV DNA after it had been undetectable. Virologic breakthrough may be followed by biochemical breakthrough, defined as increased ALT levels in a patient who previously had normalized ALT levels. It may also be seen in HBV flares and hepatic decompensation if salvage therapy is not initiated promptly. Virologic breakthrough during nucleos(t)ide analogue treatment may be a result of antiviral drug resistance or medication nonadherence or cessation. Patients with virologic breakthrough should be counseled regarding medication adherence and breakthrough confirmed by retesting for serum HBV DNA levels after 1–3 months. Salvage therapy should be initiated immediately in patients who have decompensated liver disease or severe hepatitis flares, but in other patients, it can be deferred until after virologic breakthrough is confirmed to avoid unnecessary changes in medications [30]. It is important to initiate treatment with a drug or drugs that have a high genetic barrier to resistance (a low potential for drug resistance), because sequential monotherapy may result in the selection of multiple drug resistance mutations. De novo combination therapy may prevent the emergence of multiple drug resistant mutants [43].

In co-infected patients on HAART, if there is a need to stop HAART, there may be HBV viral rebound. In 147 HIV/HBV co-infected patients, ALT elevations occurred in 29% within the first 6 months after withdrawal, with 2% and 3.4% reaching grade 3 and 4 levels of liver injury [44]. If reactivation occurs, resuming an agent that is active against HBV is required. Reactivation can also be avoided by continuing anti-HBV specific agents when HAART is discontinued even if the drugs are no longer effective for HIV treatment. When changing or initiating antiretroviral regimens, it is important to continue administering anti-HBV agents, since there is a risk of immune reconstitution inflammatory syndrome (IRIS) during recovery of CD4 cell counts. IRIS may be difficult to distinguish from hepatotoxicity.

Active anti-HBV NRTIs should be administered until the desired end point is achieved. For patients who have decompensated cirrhosis, life-long treatment is recommended due to risk of fatal flares if treatment is discontinued. For patients who have compensated cirrhosis, life-long treatment is generally recommended. Discontinuation of treatment may be considered in patients who have lost HBsAg or who have completed adequate duration of consolidation therapy after anti-HBe seroconversion provided that these patients are closely monitored. Treatment should be promptly reintroduced if there is viral rebound or an ALT flare [30].

## Current HBV treatment clinical trials

There are some ongoing clinical trials that are investigating the role of combination treatment in chronic HBV infection but there are few that include HIV/HBV co-infected patients.

**TDF versus TDF plus FTC:** This National Institute of Health (NIH) study will test whether the combination of two medications, TDF and FTC, are safer and more effective fortreating chronic HBV than TDF alone.

**PEG IFN α-2a plus ETV versus ETV alone for HBeAg positive chronic HBV patients:** This open-label, randomized, comparative, multi-center clinical trial objective is to restore host immunity against HBV and to explore if prolonged ETV can maximize viral suppression. Genotypic and virologic resistance to ETV will also be assessed at baseline and at end of years 1, 2 and 3. The primary efficacy will be HBeAg seroconversion.

**Efficacy and safety of TDF in combination with PEG IFN α-2a versus standard of care TDF monotherapy or PEG IFN α-2a monotherapy for 48 weeks in chronic HBV:** The purpose of this study is to evaluate the safety and efficacy of TDF plus PEG IFN α-2a

combination therapy versus standard of care TDF monotherapy or PEG IFN monotherapy in non-cirrhotic chronic HBV subjects as determined by loss of HBsAg at Week 72 following 48 weeks of treatment.

**Efficacy and safety study of ETV plus TDF in patients with chronic hepatitis B who failed previous treatment:** The purpose is to show that the combination of ETV and TDF will be safe, well tolerated and effective in chronic HBV patients who have failed previous treatment by measuring the proportion of subjects who achieve a virological response defined as HBV DNA <50 IU/mL at Week 48.

**Randomized controlled study of TDF plus LdT versus monotherapy with either drug in HBeAg Negative chronic HBV patients:** This is an open labeled, prospective, randomized, multicentered study to determine the efficacy and safety of combination of TDF plus LdT versus monotherapy with either drug alone over 104 weeks (Figure 1).

## Vaccination

Immunization with hepatitis A virus (HAV) and HBV vaccine is recommended for all HIV infected individuals without immunity to HAV or HBV. Factors associated with this impaired HBV vaccine response in HIV-infected individuals may include older age, uncontrolled HIV replication, and low nadir CD4 cell count [45-48]. HBV vaccine should be given when CD4 cell counts are >200 cells/μl as response to vaccine is poor below this level. Persons with CD4 cell counts below 200 cells/μl should receive HAART first and HBV vaccine when CD4 cell counts rise above 200 cells/μl [28]. Post vaccination testing for anti-HBs is recommended and vaccine nonresponders should undergo repeat immunization with a full series. De Vries-Sluijs reported double dosed HBV revaccination of HIV infected patients proved to be effective in 50.7% [49]. Addition of CPG 7909 (an immunostimulatory toll like receptor 9 (TLR9) agonist oligonucleotide used as an adjuvant) achieves rapid, higher, and sustained HBV seroprotection and increases HBV specific T helper cell response to HBV vaccine in HIV subjects. These results confirm a potential adjuvant role for CPG 7909 in vaccine hyporesponsive populations including those living with HIV [50].

## HIV and HCV co-infection

Liver disease remains one of the leading causes of non-AIDS mortality in the HIV infected individual. HCV leading to liver cirrhosis is the leading cause of liver transplantation in the US [51]. HIV and HCV co-infection has significant clinical implications and raises many challenging issues for patients and their health care providers [52].

Recent studies support current recommendations to begin ART early in the course of HIV infection in order to limit progression of liver disease in co-infected patients. HIV co-infection has a negative impact on HCV pathogenesis and despite increased risk of drug-related hepatotoxicity, successful response to ART might lessen progression of chronic liver disease and improve response to anti-HCV therapy [53]. Co-infected patients have higher rates of morbidity and mortality related to ESLD [54,55]. During the chronic stage of either HIV or HCV infection, a relatively stable viral load or "set point" is maintained. However, in the setting of combined infection, HCV RNA levels increase after HIV seroconversion and continue to increase over time compared with patients with HCV alone [56,57]. The level of HCV viremia is inversely correlated with lower CD4 counts in most, but not all studies [57,58] and may transiently increase with initiation of antiretroviral therapy (as seen with IRIS) or with heavy alcohol use [59]. Overall increases in the HCV viral load do not alter the severity of liver-related disease but do have an impact on treatment response. Another way HIV infection may increase HCV replication is through the virus itself. An *in vitro* study demonstrated that the envelope protein of HIV (gp120) increased HCV replication through engagement of cellular co-receptors of HIV (e.g. chemokine receptor type 4 (CXCR4) or chemokine receptor type 5 (CCR5)) [60]. Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) receptors may also be involved independently by both HIV and HCV that result in the killing of hepatocytes and this may suggest a pathogenic model to understand why HIV/HCV co-infection accelerates liver injury [61].

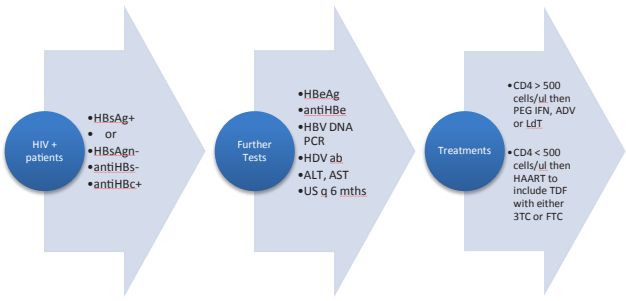



**Figure 1:** Treatment algorithm for HIV/HBV co-infected.

HIV infected patients have lower rates of spontaneous virologic clearance during acute infection that may be due to impaired lymphoproliferative responses to HCV antigens [62,63]. Patients with hepatitis C and underlying HIV progress faster to cirrhosis than patients with hepatitis C alone [64,65]. Risk factors associated with higher rates of advanced fibrosis include alcohol use, age and low CD4 T-cell counts <200 cells/μl [64,66].

HIV replicates in many cell types in addition to CD4+ T-cells [67]. More controversial is whether HCV also replicates in extra hepatic sites such as peripheral blood mononuclear cells (PBMCs) [68]. While some studies have documented HCV RNA negative strands (the viral replicative intermediate) in peripheral blood mononuclear cells (PBMC), others have not confirmed this finding [69,70]. It has been suggested that HCV RNA replication in PBMCs may occur in HIV/HCV co-infected patients, but not in those with HCV alone [71]. HCV has also been isolated from cervicovaginal lavage fluid [72] in HIV infected women but not in women with HCV alone [73]. This may partially explain the increase in HCV activity and sexual transmission in HIV co-infected patients.

HIV infected patients who are also infected with HCV have higher levels of HCV in the blood, more rapid progression to HCV related liver disease and increased risk for cirrhosis and HCC [64,74-76]. HCV is considered an opportunistic infection (although not AIDS defining) in HIV infected patients. Co-infected patients have higher levels of HCV RNA than HCV only infected patients. Titers usually correlate with the CD4 count. Patients with HIV/HCV co-infection may also have more severe liver damage (higher score of piecemeal necrosis and higher stage of fibrosis) than those without HIV infection.

Data from the United States and Europe suggest that hepatocellular carcinoma (HCC) occurs at a younger age and is associated with shorter survival in HIV/HCV co-infected patients compared with those with HCV infection alone [77]. In addition, a multicenter study in the United States and Canada also confirmed that progression from initial HCV infection to HCC was significantly faster in co-infected patients (26 years) than in HCV monoinfected patients (34 years) [78].

Single-stranded RNA viruses, like HIV and HCV, lack proofreading

mechanisms resulting in high mutational rates [79] which lead to the formation of genetically distinct viral variants that collectively comprise a "quasispecies." Whether a particular nucleotide substitution results in a replication competent mutant depends on the involved site.

During replication of HCV, RNA dependent RNA polymerase frequently introduces random nucleotide errors, resulting in a high rate of spontaneous nucleotide substitutions [80].

These similarities between HIV and HCV viral diversity have treatment implications. The extent of the quasispecies evolution in an individual and the level of viremia have been implicated as predictors of response to IFN [81,82]. In one study of HIV/HCV co-infected patients, lower quasispecies complexity of HCV was associated with earlier viral clearance in response to interferon based regimens [83]. Furthermore, there is evidence of different evolution of the quasispecies of HCV in various compartments as has been noted for HIV [84].

The potential for HCV drug resistance parallels that of HIV, as demonstrated with the introduction of specifically targeted antiviral therapies against HCV (STAT-C) [85]. As described in the past with HIV, resistance mutations to specific HCV protease and polymerase inhibitors have been identified even in treatment naive HCV and HIV/HCV co-infected patients [86,87]. These issues will become more important with the introduction of STAT-C agents into clinical practice in the future.

## Epidemiology

HCV is a RNA flavivirus that infects 4 million (1.8%) people in the United States and 150-200 million worldwide [88]. Co-infection with HIV and HCV is common since both infections share similar routes of transmission. In the United States, approximately 30% of patients who are HIV-infected are also co-infected with HCV [89]. Main routes of Hepatitis C transmission include IVDU (Intravenous Drug Users), transfusion of blood products, needle sticks and to a lesser extent sexual intercourse (although rates are rising due to anal intercourse especially in MSM). Since the relative efficiency of transmission differs according to route, the prevalence of co-infection varies markedly among various risk groups. In one clinical trial, HCV seroprevalence in HIV infected patients ranged from 73% in intravenous drug users to only 4% in patients considered to be at low risk [90]. The sequence of infections also tends to aggregate by transmission route. For example, IVDU usually acquire HCV before HIV infection while MSM typically are infected with HIV before they acquire HCV infection [91].

HCV is transmitted efficiently via percutaneous routes, so seroprevalence rates are highest in IVDU and hemophiliacs who received contaminated blood products prior to the introduction of HCV screening in 1990. IVDU is currently the leading route of HCV transmission in the United States since the risk of transfusion HCV infection is now very low. Approximately 50 to 90 percent of IVDU are infected with HCV after sharing contaminated needles or drug paraphernalia [92]. Among heterosexual partners, HIV is much more easily transmissible than HCV via intercourse [93,94]. The risk of HCV transmission is exceedingly low in monogamous couples [95], but appears to increase in patients who report multiple sexual partners [92]. In MSM, unprotected anal sex, fisting, group sex, and recreational drugs (e.g. gamma hydroxy butyrate (GHB)) [96] are associated with HCV acquisition [97,98]. The importance of mucosal damage as a risk factor for HCV acquisition was highlighted in a report in which 18 of 20 MSM reported either genital ulcerative disease (lymphogranulomavenereum, syphilis, or HSV-2) or fisting within the period of acute HCV seroconversion [99].

Vertical transmission of HCV appears to be facilitated by HIV co-infection. A meta-analysis of 10 studies demonstrated that maternal co-infection increases the odds of vertical HCV transmission by approximately 90 percent (odds ratio (OR) 1.9; 95% confidence interval (CI) 1.4-2.7) compared with maternal HCV infection alone [100]. There are rare case reports of health care workers who have simultaneously acquired HIV and HCV via percutaneous exposure [101].

HIV/HCV co-infected patients have accelerated rates of fibrosis compared with patients with HCV alone. Insight into the mechanisms that underlie the immunopathogenesis of these persistent viral infections could lead to new therapeutic strategies. Liver fibrosis progression may be related to weak cellular immune responses to HCV antigens in HIV infected patients. HIV infection is characterized by marked decreases in the number of circulating CD4 cells, functional impairment of both CD4 and CD8 cells and down-regulation of CD28 expression (a co-stimulatory molecule required for effective lymphocyte activation) [102]. Patients with lower CD4 cells have less HCV specific CD8 cells responses and this could explain the more advanced liver disease progression since CD8 cells responses are thought to be of primary importance in the immune response to viral infection. The successful administration of HAART may restore cellular immune responses to HCV antigens [103].

## HCV genotypes

There are 6 HCV genotypes found worldwide. Most of the clinical trials of HCV therapy have enrolled patients with HCV genotype 1, 2, 3 or 4 infections. Genotype 1 (A/B) is predominant in North America and also the least responsive to IFN based treatment [104]. HCV genotype 1 and 4 are less IFN responsive than HCV genotypes 2 or 3.

## Laboratory data and progression

All HIV infected persons should be screened for HCV infection using enzyme immunoassays. Those with antibody to HCV should have quantitative HCV RNA testing to confirm the presence of viremia and serve as a baseline prior to therapy initiation [78]. Some patients with more advanced immunosuppression (e.g.CD4<100cells/µl ) may have a false negative serology test (about 5%) and should be screened further with HCV RNA testing especially if they have risk factors of HCV acquisition such as injection drug use [105-107].

In patients with suspected acute HCV infection, an HCV antibody and HCV RNA level should both be obtained since viremia precedes seroconversion. HCV antibody is detected approximately 8 to 12 weeks after infection although delayed antibody responses have been described in one small study of 43 HIV infected patients [88,108]. Baseline laboratory investigation in co-infected patients should include: HCV quantitative RNA and genotype, aminotransferases, bilirubin, alkaline phosphatase, complete blood count, prothrombin time and albumin, glucose (insulin resistance can be associated with poorer response), creatinine, thyroid function tests, absolute CD4 counts and percentage, HIV quantitative RNA, HAV IgG antibody and HBV serology (HBsAg, anti-HBc, anti-HBs) as well as a pregnancy test for women of childbearing potential.

The utility of non-invasive markers is under active clinical investigation in HIV/HCV co-infected patients as a marker of fibrosis [109]. Some of these non-invasive tests use specialized markers such as α-2 macroglobulin (e.g. Fibrotest or Fibrosure). Imaging is particularly important in patients with cirrhosis in whom there is an increased risk of hepatocellular carcinoma. AASLD recommends that patients with cirrhosis undergo surveillance for HCC with US every 6 to 12

months. Combined use of AFP and US increases detection rates, but also increases cost and false-positive rates. All HCV-infected patients with cirrhosis should also have endoscopy to screen for the presence of varices.

## HAART considerations in HIV/HCV co-infected patients

The goal of treating hepatitis C is to achieve a sustained virological response (SVR) that is defined as undetectable HCV RNA six months after the completion of treatment. Chronic viral hepatitis increases the risk of hepatotoxicity from antiretroviral therapy [110]. The pathogenesis of HAART associated hepatotoxicity may be related to IRIS that manifests itself as hepatocyte necrosis with a concomitant rise in CD4 count. Through viral eradication, improvement in fibrosis and necro-inflammation may be seen and also the risk of hepatocellular carcinoma may be decreased. Another potential benefit may be reduced risk of HAART associated hepatotoxicity with sustained HCV clearance [111]. The failure to achieve a SVR in co-infected patients was associated with an increased risk of overall mortality, liver related mortality and hepatic decompensation [76,112].

The decision to treat an HIV infected patient for HCV infection will depend on the stage of liver disease (e.g. portal fibrosis or higher stage), patient readiness and the presence of comorbidities. Treatment for mild disease (e.g. portal fibrosis) is justified since patients with HIV have faster fibrosis progression rates than patients with HCV alone [113]. Excellent treatment candidates include those with acute HCV as well as those with chronic HCV with low levels of HCV RNA and favorable HCV genotypes (2 or 3). Such patients may be considered candidates for PEG IFN/ribavirin (RBV) therapy if they are motivated to be treated, regardless of their stage of disease. In the more difficult-to-treat patient (e.g. high HCV RNA with genotype 1 or 4 infection), staging of disease (e.g. liver biopsy or non-invasive fibrosis markers) may be helpful to determine the urgency of this decision. Regardless of whether the patient agrees to HCV therapy or not, staging of liver disease should be performed. Patients with portal fibrosis or more advanced disease should be counseled regarding the potential benefits of virologic clearance and the potential risks of progressive liver disease, if untreated. The following patients are NOT candidates for PEG IFN/RBV therapy: history of decompensated cirrhosis, pregnancy or inability to prevent pregnancy, uncontrolled depression, and unstable cardiac and pulmonary conditions or CD4 cell counts < 200 cells/μl.

## HCV treatment initiation in HIV co-infected patients

Several observational studies have noted a reduced rate of liver-related mortality in patients taking HAART compared with those who are not [76]. In the patient with advanced AIDS (CD4 count <200 cells/μl), HAART and prophylaxis for opportunistic infections should be initiated first to decrease the overall risk of morbidity and mortality. Treatment for HCV can be initiated later when the patient has attained HIV suppression and immunologic improvement. In patients with CD4 cell counts between 350 and 500 cells/μl, it is best to first initiate HAART to assess any potential adverse events related to antiretroviral medications. HCV therapy can be started 4-6 weeks later. There are certain patient subsets where a trial of HCV therapy should be considered before initiation of HAART. The International AIDS Society-USA Panel suggests that PEG IFN/RBV should be administered before consideration of HAART among patients who have CD4 cell counts >500 cells/μl and HCV genotypes 2 or 3 infection. This recommendation is based on the relative efficacy of PEG IFN and RBV in patients with these favorable genotypes. However, this rationale could also be extended to HIV infected patients with low viral load genotype 1 and 4 infections, where viral eradication rates have been comparably high as well as acute HCV seroconverters. If the patient attains viral eradication, then HAART can be postponed. Viral clearance of HCV is associated with a decreased risk of liver related morbidity and mortality and lower overall mortality [112].

Standard IFN and RBV have been used as combination therapy for the treatment of HCV infected patients since 1998, when it was demonstrated that the addition of RBV led to significantly higher rates of viral clearance than IFN alone and much lower rates of relapse after treatment discontinuation [114]. The next major advance in the treatment of HCV was the development of PEG IFN. "Pegylation" refers to the addition of a polyethylene molecule to the native protein that decreases excretion of IFN and thereby increases the half-life. PEG IFN/RBV combination therapy has significantly improved overall SVR rates to greater than 55% in mono-infected HCV patients compared with earlier rates of approximately 35 percent achieved with standard therapy. However, response rates in patients with genotype 1 are generally lower than in patients infected with genotype 2 or 3. In the largest treatment trial to date in HIV/HCV co-infected patients (APRICOT), the overall SVR rate was 40% with the PEG IFN/RBV arm compared with 20% with PEG IFN monotherapy and 12% with standard IFN/RBV [115].

In patients infected with HCV genotype 1, the rates of SVR were 29% with PEG IFN α-2a plus RBV, 14% with PEG INF α-2a plus placebo, and 7% with IFN α-2a plus RBV [115]. The corresponding rates in patients infected with HCV genotype 2 or 3 were 62%, 36%, and 20% respectively [115].

Two new HCV specific protease inhibitors which target the nonstructural protein 3/4A (NS3/4A) serine protease, boceprevir and telaprevir, were FDA approved in May 2011 for use in combination with PEG IFN/RBV in HIV seronegative patients with HCV genotype 1 infection leading the way for trials in the co-infected population.

## Predicting IFN response – IL28B

One of the most important predictors of outcome is genotype. Mono-infected HCV patients with genotype 2 or 3 infection have higher sustained virologic response rates than patients with genotype 1 or 4 infection (e.g. 75 to 80% compared with 42 to 46%). This observation holds true for HIV/HCV co-infected patients with response rates for genotype 2 and 3 infection range from 44 to 73% compared with 17 to 29% or genotype 1 infection [115,116]. Another important predictor of treatment response is baseline HCV RNA [117]. Of note, multiple studies have demonstrated that HIV/HCV co-infected patients generally have higher HCV RNA levels than patients with HCV alone that may contribute to slower rates of viral clearance [118].

A complete early virologic response (EVR) is defined as total viral suppression at 12 weeks whereas a 2 log drop in viremiais a partial EVR. As shown in patients with HCV alone, the absence of an EVR is a powerful negative predictor of a SVR in HIV infected patients [119]. This is well illustrated in a multicenter, placebo-controlled trial (RIBAVIC) which compared standard IFN/RBV to PEG IFN/RBV in 412 HIV/HCV co-infected patients. Only 1% of patients who did not achieve a partial or complete EVR were able to achieve a SVR [116].

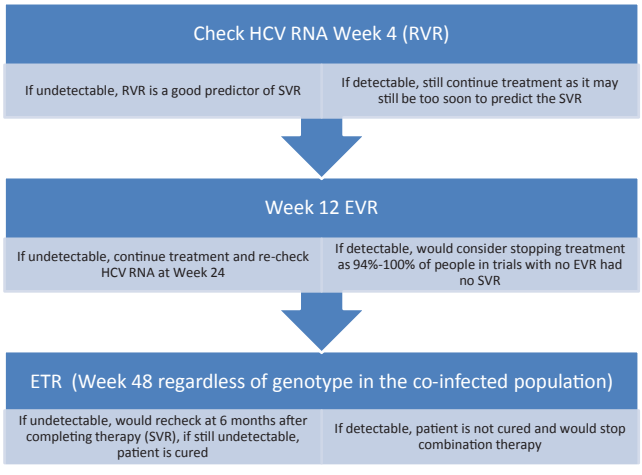
Attainment of a non-detectable HCV RNA at four weeks (rapid viral response (RVR)) is also a powerful positive predictor of a SVR in patients with HCV alone. This was studied in patients in the APRICOT trial [115] which showed that in 289 patients with genotype 1 infection, 22 (13%) had a RVR and that 18 of these 22 patients (85%) went on to achieve a SVR.

Genome-wide association studies have identified several single nucleotide polymorphisms (SNPs) around the IL28B gene (which codes for IFN-lambda 3) which are strongly associated with treatment induced viral clearance of genotype 1 infection in HIV/HCV co-infected patients (i.e. IL28B genotype CC) [120,121]. IL28B TT/CT genotypes are associated with poorer response to IFN based treatment. IL28B TT/CT genotypes are observed at a higher rate among African American individuals [122]. The role of this genotype in predicting a patient's response to HCV therapeutics without interferon is unknown. In patients with HCV alone, treatment duration with PEG IFN/RBV is generally for 24 weeks for patients with genotype 2 or 3 and 48 weeks for genotype 1 or 4. Most of the larger clinical trials of HCV therapy in HIV infected patients have been designed with 48 weeks of treatment, regardless of genotype (Figure 2).

## HIV/HCV treatment clinical trials

IFN is an immunomodulatory agent that stimulates host antiviral genes whereas the mechanism of action for RBV is not well understood. For PEG IFN α-2b, weight-based dosing (1.5 mcg/kg) is employed. For PEG IIFN α-2a, a standard dose of 180 mg/kg is used, regardless of weight. Both are administered once weekly via a subcutaneous route. In patients with HCV alone, RBV is administered at a fixed dosing of 400 mg twice daily for genotype 2 or 3 infection, whereas weight-based RBV (approximately 13 mg/kg in two divided doses) is preferred in patients with genotype 1 and 4 infection due to improved efficacy in patients with these more "difficult-to-treat" genotypes.

There is no data on the use of boceprevir/pegylated interferon/ribavirin for HCV genotype 1 infection among HIV-infected patients. ACTG 5178, also known as "SLAM-C" (Suppressive Long-term Antiviral Management of HCV and HIV co-infected patients) enrolled 330 USA patients who did not achieve a virologic response on prior treatment for HCV. Results from this trial do not support the use of maintenance therapy in patients who have not responded to treatment for HCV. However, the study results suggest that HAART may have some benefit in slowing down fibrosis progression. In a controlled trial, 60 HIV/HCV genotype 1 co-infected patients were randomly assigned to 12 weeks of PEG IFN α-2a plus RBV plus placebo or PEG IFN α-2a, RBV plus telaprevir [123]. Patients in both arms received an additional 36 weeks of PEG IFN with RBV. RBV was dosed as 400 mg twice daily in both arms. Patients in part A of the trial were not on HAART while patients in part B were on predetermined HAART regimens that included TDF/FTC plus either efavirenz (EFV) or ritonavir (RTV) boosted atazanavir (ATV). Telaprevir was dosed as 750 mg every eight hours except when administered with EFV. In patients who took EFV, telaprevir was dosed as 1125 mg every eight hours. Sixty-eight percent had genotype 1a, 32% genotype 1b and 83% had a high viral load (>800,000 IU/mL) and 10% had advanced liver fibrosis on biopsy. An interim analysis was performed of the 59 of 60 patients who received treatment. Significantly greater proportions of patients assigned to the telaprevir arm had achieved RVR at four weeks compared with the standard of care arm (70 percent versus 5 percent, respectively). Of the 41 patients who reached the 12 week point, greater proportions of patients assigned to the telaprevir arm achieved viral suppression at 12 weeks compared with the standard of care arm (68 versus 14 percent, respectively). Common side effects in the telaprevir arm included pruritis, rash, nausea, vomiting, anorexia, and dizziness.




RVR=Rapid Virologic Response (undetectable HCV Viral load at 4 weeks)

EVR=Early Virologic Response (≥ 2 log decline or HCV RNA < 600 IU/mL)

ETR=End Treatment Response (undetectable HCV viral load at the end of treatment)

SVR=Sustained Virologic Response (undetectable HCV RNA at 24 weeks after the end of treatment)

**Figure 2: Algorithm for the Treatment of HIV/HCV Co-Infection.**

Characterization of HCV encoded proteins and their function has permitted development of strategies aimed at interrupting HCV replication. Telaprevir and boceprevir target the NS3/4A serine protease. Other key potential drug targets include the nonstructural 2/3 (NS2/3) autoprotease, the nonstructural 3 (NS3) RNA helicase and the nonstructural 5B (NS5B) RNA dependent RNA polymerase (RdRp). The strategy of targeting HCV encoded proteins with small molecule inhibitors has been referred to as direct acting antiviral (DAA) therapy or specifically targeted antiviral therapy for HCV (STAT-C).

The HCV RNA genome encodes a single polyprotein of approximately 3000 amino acids. This polyprotein is cleaved during and after translation by both host and viral encoded proteases into the ten mature viral proteins. The NS3/4A viral protein contains a serine protease activity that is required for cleavage of the viral polyprotein at four sites. Telaprevir and boceprevir are both NS3/4A serine protease inhibitors.

The phase IIb Protease Inhibition for Viral Evaluation (PROVE) trials 1 and 2 evaluated combination therapy with PEG IFN plus RBV in treatment-naïve patients with chronic genotype 1 infection [124,125] whereas a third trial, PROVE 3, looked at the use of telaprevir in patients who had failed previous antiviral therapy.

In PROVE 1, a total of 263 patients were randomly assigned to one of three telaprevir groups or to a control group. The control group (PR48) received PEG IFN α-2a (180 mcg each week) and RBV (1000 or 1200 mg daily according to body weight) for 48 weeks plus placebo for the first 12 weeks [124]. The three telaprevir groups all received the same dose of telaprevir (1250 mg on day 1 and 750 mg every eight hours thereafter) for 12 weeks along with either 12 (T12PR12), 24 (T12PR24), or 48 (T12PR48) weeks of PEG IFNα-2a plus RBV. The SVR rate was significantly higher in the T12PR24 and T12PR48 telaprevir groups compared with the control group (61% and 67% versus 41%, respectively). However, the rate of discontinuation because of adverse events (mainly rash) was significantly higher in all three telaprevir groups (21% versus 11% in the control group).

In PROVE 2, a total of 334 patients received one of the following regimens [125]:

1. Telaprevir (1250 mg on day one then 750 mg every eight hours) and PEG IFN α-2a (180 mcg each week) for 12 weeks (T12/P12)
2. Telaprevir plus PEG IFN α-2a plus weight-based RBV for 12 weeks (T12/PR12)
3. Telaprevir plus PEG IFN α-2a plus weight-based RBV for 12 weeks followed by PEG IFN α-2a/RBV for an additional 12 weeks (T12/PR24)
4. Standard of care PEG IFN α-2a/RBV for 48 weeks (PR48)

A SVR was achieved in 69% and 60% of patients in the T12/PR24 and T12/PR12 arms, respectively, while the SVR was 46% in the standard of care PR48 arm and only 36% in the T12/P12 arm. The difference was statistically significant for the comparison between the T12PR24 versus control arms (69% versus 46%, respectively). Adverse events occurred significantly more frequently in telaprevir treated patients. In particular, 12 percent of patients across all telaprevir treatment arms discontinued therapy due to skin rash. These data suggest that in treatment-naïve patients, the combination of telaprevir with PEG IFN α-2a/RBV may significantly increase SVR rates compared with PEG IFN α-2a/RBV alone with the possible additional benefit of a shorter course of therapy.

In PROVE 3, telaprevir was given to 453 chronic (genotype 1) HCV patients who had been non-responders or who had relapsed with prior therapy with PEG IFN α-2a/RBV [126]. Forty-three percent of subjects had cirrhosis or bridging fibrosis. The treatment regimens studied were (1) T12/PR24, (2) T24/PR48, (3) T24/P24, no ribavirin, or (4) standard of care PR48. The overall SVR rates were 51%, 53%, 24%, and 14% in the T12/PR24, T24/PR48, T24/P24, and PR48 arms, respectively. Comparing these four arms by subgroup, the SVR rates were 69%, 76%, 42%, and 20% in those with previous relapse, 57%, 62%, 36%, and 40% in prior breakthroughs, and 39%, 38%, 11%, and 9% in prior non-responders. Treatment was discontinued due to adverse events in 15% of patients who received telaprevir with PEG IFN α-2a/RBV compared with 4 percent of patients who received PEG IFN α-2a/RBV alone.

Boceprevir is a competitive inhibitor of the NS3 protease complex of HCV genotype 1. As such, it does not have significant activity against other HCV genotypes [127,128]. A phase II study (HCV SPRINT-1) that included 595 treatment naïve patients with genotype 1 HCV compared the following treatment regimens: (1) PEG IFN α-2b/ weight-based RBV (800 to 1400 mg daily) for four weeks followed by the addition of boceprevir for either 24 or 44 more weeks (lead-in), (2) boceprevir/PEG IFN α-2b/low dose RBV (400 to 1000 mg daily) for 28 or 48 weeks (no lead-in), or (3) standard of care PEG IFN α-2b/RBV for 48 weeks [129]. In a second part of this study, low-dose RBV (100 to 400 mg daily) was compared with full-dose RBV (800 to 1400 mg daily) in combination with boceprevir and PEG IFNα-2bfor 48 weeks. The 48-week boceprevir lead-in group achieved an SVR rate of 75% versus 38% for the standard of care group. The twenty-eight week boceprevir lead-in group had an SVR of 56%. The 48 and 24week no lead-in groups had SVR rates of 67% and 54% respectively. In part 2 of SPRINT-1, the low-dose RBV group had an SVR of only 36% compared with 50% for the full-dose RBV group. This showed that the lead in initially withPEG IFN α-2b/RBVwas important to reduce the viral load to enhance the response to boceprevir.

Conclusions that could be drawn from these clinical trials include that RBV appears to significantly reduce relapse rates even in protease inhibitor regimens and will therefore continue to be an important component of protease inhibitor regimens. Patients with severe chronic kidney disease or prior known intolerance to RBV are therefore much less likely to benefit from protease inhibitor therapy. While protease inhibitors substantially increase SVR rates in genotype 1 chronic HCV, patients should be made aware that approximately 20 to 30 percent of treatment-naïve individuals with genotype 1 infection maynot achieve an SVR with combination protease inhibitor/PEG IFN/RBV. This is even more significant for null responders to prior PEG IFN/RBV treatment in whom only 30% to 40% will likely attain a SVR even with the addition of a protease inhibitor [126].

A number of other protease inhibitors are currently in phase I/II clinical development including: danoprevir (ITMN-191/ RG7227, Roche), TMC435350 (Medivir/Tibotec), BI 20133 (BoehringerIngelheim), vaniprevir (MK-7009, Merck), BMS-650032 (Bristol-Myers Squibb), ABT-450 (Abbott/Enanta), TMC435 (Tibotec), VX-813 and VX-985 (Vertex).

One of the features of HCV that increase its ability to develop viral resistance mutations to DAA therapy, also known as STAT-C therapy, is the error-prone nature of the RdRp. Therefore, it is not surprising that all of the current DAA compounds in phase III clinical trials are being used in combination with PEG IFN and RBV, since combination therapy appears to substantially lower the risk of viral resistance and on-treatment virologic breakthrough [85].

## DAA without PEG IFN/RBV

While the first generation of DAA drugs will likely be used only in combination with PEG IFN/RBV, there are a substantial number of patients who cannot receive PEG IFN or RBV due to a known intolerance or contraindication (e.g. severe chronic kidney disease or depression).

The first study to address this question was an ascending dose phase I study called INFORM-1, combining the protease inhibitor danoprevir (ITMN-191/ RG7227) and the nucleoside analog protease inhibitor RG7128 [130]. The effect of the combination of ITMN-191/RG7227 and RG7128 appeared to be additive. No treatment-related serious adverse events, dose reductions, or discontinuations were reported for this short dosing period.

## Other future therapeutic options and targets

**Polymerase inhibitors: Inhibitors of the NS5B RdRp fall into two broad classes:** nucleoside analogs and non-nucleoside inhibitors (NNIs). Nucleoside analogs bind to the NS5B active site while NNIs bind to one of at least three allosteric binding pockets outside the active site. Binding of the NNIs to one of these allosteric binding pockets results in a conformational change in the active site thereby inhibiting RNA polymerase activity. Unfortunately, development of a number of promising HCV polymerase inhibitors has been halted due to toxicity. R1626 (Roche), for example, was abandoned due to high rates of neutropenia.

**NS5A inhibitors:** The HCV NS5A protein is essential for viral replication and for the assembly of infectious virions, although the precise molecular mechanisms by which NS5A accomplishes these functions are uncertain [131].

**Cyclophilin inhibitors:** Cyclosporin A, an immunosuppressant, inhibits HCV replication in cell culture replicon models [132]. The antiviral effect of cyclosporin A is due to its inhibition of the cellular protein cyclophilin B [133]. Cyclophilin B, in turn, interacts with NS5B and appears to promote its RNA binding activity.

**Nitaxozanide:** Nitazoxanide is an antiprotozoal drug approved

for the treatment of Cryptosporidium parvum and Giardia lamblia diarrhea. However, it also has broad anti-infective activity against organisms as diverse as helminths, Clostridium difficile and several viruses. Nitazoxanide inhibits both HBV and HCV replication in cell culture models [134]. The mechanism of nitazoxanide activity against HCV may be mediated by phosphorylation of the host proteins kinase R and eIF2α, which in turn inhibits HCV replication [135]

### Importance of treating acute hepatitis C

Treatment outcome among 50 HIV infected MSM with acute HCV infection in Amsterdam was evaluated [136]. Overall sustained virological response (SVR) rate was 76%. Treatment duration was not significantly associated with SVR, suggesting that a 24 week treatment may be sufficient for acute HCV infection in HIV co-infected patients as compared to a 48 week treatment. The SVR was also not affected by the genotype as patients with genotype 1 had a SVR of 74%. The regimens used in this study were the combination of PEG IFN α-2a and RBV.

## Conclusion

HIV co-infected HBV and HCV patients present great challenges in management for the clinician. Knowledge of the complex interactions of these viruses as well as the effect of various treatment modalities on each virus is key to understanding and treating these patients effectively. New laboratory tests and therapeutic options make this an exciting time to care for these patients and offers great hope of a cure.

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